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Effects of Dopamine- and Serotonin-Related Compounds on Methamphetamine-Induced Self-Injurious Behavior in Mice

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Abstract. Methamphetamine induces hyperlocomotion, and high doses of methamphetamine induce self-injurious behavior (SIB) in rodents. It is well known that the monoaminergic system is involved in methamphetamine-induced behavior. However, the effects of dopamine- and serotonin (5-HT)-related compounds on high-dose methamphetamine-induced behavior have not been sufficiently clarified. Therefore, the present study was designed to investigate the effects of dopamine receptor antagonists and indirect 5-HT receptor agonists on high-dose methamphetamine-induced behavior in mice. Methamphetamine (20 mg/kg) initially increased locomotor activity. As the dosage increased, continuous SIB accompanied by a reduction in locomotor activity was observed. The hyperlocomotion and SIB induced by 20 mg/kg of methamphetamine was abolished by high doses of SCH23390 and haloperidol, indicating that the hyperlocomotion and SIB induced by high doses of methamphetamine are mediated by the activation of D_1- and D_2-receptors. Furthermore, haloperidol (0.1 mg/kg) potently increased locomotor activity in combination with 20 mg/kg methamphetamine. These results suggest that excess dopaminergic activation, especially activation of dopamine D_2-receptors, may be involved in the decrease in locomotor activity induced by a high dose of methamphetamine. On the other hand, indirect 5-HT receptor agonists attenuated methamphetamine-induced SIB, suggesting that the stimulation of 5-HT receptors plays an important role in high-dose methamphetamine-induced SIB in mice.

Keywords: methamphetamine, self-injurious behavior, dopamine, serotonin

Introduction

Self-injurious behavior (SIB) in humans consists of self-biting, head banging, face slapping, skin picking, and scratching. These behaviors have been observed in several neuropsychiatric disorders, including schizophrenia, Lesch-Nyhan syndrome (1 – 3), Tourette's syndrome (4, 5), and Cornelia de Lange syndrome (6). Although the neuronal mechanisms that underlie SIB remain unclear, imbalances in various neurotransmitter systems, including brain dopamine, serotonin, and opioid systems, may be provisionally linked to this disorder (7, 8).

Methamphetamine is a prototypic psychostimulant and is significantly abused worldwide. After long-term use, the dose of psychostimulants is often increased; therefore, the permanent (i.e., toxic) effects of psychostimulants are of concern. Among the undesirable effects of psychostimulants that are seen with large doses is psychostimulant-induced psychosis (9). In rodents, it is well known that methamphetamine induces hyperactivity, stereotyped behavior, and rewarding effects. Psychostimulants increase the release of dopamine not only but also norepinephrine and serotonin (5-HT) from the nerve terminal. A great deal of evidence suggests that the dopaminergic system is involved in several behavioral effects of psychostimulants. Previous studies have shown that relatively high doses of psychostimulants induce SIB in rats and mice (10 – 12).

Dopamine deficiencies may be related to the SIB in

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Lesch-Nyhan patients (13). 5-HT has also been implicated in SIB, since some Lesch-Nyhan patients exhibit the amelioration of SIB symptoms following the administration of 5-hydroxytryptophan (5-HTP), a precursor of 5-HT (1, 14). Since 5-HT has been widely implicated in the expression of SIB, it is noteworthy that selective 5-HT reuptake inhibitors (SSRIs) have been reported to be beneficial for alleviating SIB in Prader-Willi syndrome (15). In fact, previous studies have demonstrated that monoamine-related compounds could attenuate psychostimulant-induced SIB in rodents (16, 17). Therefore, the first aim of the present study was to investigate the effects of dopamine and 5-HT-related compounds on methamphetamine-induced SIB in mice.

The analysis of the effects of drugs on locomotor activity and exploratory behavior is an important tool in behavioral pharmacology. Although they may be considered simplistic or even uninformative, changes in these parameters have important consequences in more specific processes, such as memory function and reinforcing effects, and can provide a better understanding of drug interactions. A previous study showed that high doses of methamphetamine, but not moderate doses, decreased locomotor activity (16). However, the mechanism(s) of the high-dose methamphetamine-induced decrease in locomotor activity remains unclear. Therefore, the present study was also designed to investigate the effects of monoamine-related compounds on methamphetamine-induced locomotor activity in mice.

Materials and Methods

Animals

Male ddY mice (Nihon SLC, Shizuoka) weighing 28 – 33 g were used for the following experiments. The animals were housed at a room temperature of 22.5 ± 2.5°C under a 12-h light-dark cycle (lights on at 8:00 AM). Food and water were available ad libitum. All procedures were conducted in accordance with the guiding principles for the care and use of laboratory animals by The Japanese Pharmacological Society and with the guidelines of animal care in our laboratories, as approved by the Tokyo Women's Medical University Committee on animal care and use.

SIB score and locomotor activity

The SIB score and locomotor activity were measured while each mouse was in a transparent acrylic cage (270 × 440 × 187 mm, w × l × h) on sawdust, 0.5 cm-deep, using an MK-ANIMEX activity meter (Muromachi Kikai Co., Tokyo). After an exploratory period of at least 1 h, the mice were taken out of the cage, injected s.c. or i.p. with various doses of drugs, and placed back in the cage. After the administration of methamphetamine, SIB, especially skin-picking or self-biting around the chest, was measured over 3 min at 15-min intervals. A score of 0 was given for no SIB, 1 for very mild SIB (less than 1 min), 2 for at least 1 min of SIB, and 3 for SIB almost continuously throughout the 3-min observation period. Locomotor activity was monitored in 15-min intervals for 120 min.

The doses of the drugs used were 1.0 – 20 mg/kg of methamphetamine (s.c.), 0.01 – 1.0 mg/kg of SCH23390 (i.p.), 0.01 – 1.0 mg/kg of haloperidol (i.p.), 30 – 300 mg/kg of 5-HTP (i.p.); 5.0 – 20 mg/kg of 3,4-methylenedioxymethamphetamine (MDMA) (i.p.), and 3.0 – 30 mg/kg of fluvoxamine (i.p.). In combination tests, animals were pretreated with vehicle or drugs 15 min prior to the administration of methamphetamine (20 mg/kg), and drugs were dissolved in saline in a volume of 10 ml/kg, except that 5-HTP was dissolved in 1% Tween 80 in a volume of 10 ml/kg and administered 45 min prior to the administration of methamphetamine. The doses and the pretreatment time were based on the previous papers (16, 18 – 20).

Drugs

The drugs used in the present study were methamphetamine hydrochloride (Dainippon Pharmaceutical Co., Osaka), haloperidol (Serenace Injection®; Dainippon Pharmaceutical Co.), (+)SCH23390 (Sigma Chemical Co., St. Louis, MO, USA), 5-hydroxy-DL-tryptophan (Sigma), 3,4-methylenedioxymethamphetamine (MDMA) (Sigma), and fluvoxamine maleate (TOCRIS™; Ellisville, MO, USA).

Statistical analyses

Data are expressed as the mean with S.E.M. Two-way ANOVA following Dunnet's Multiple Comparison Tests was used to evaluate the significance of differences. A P value of <0.05 determined significance.

Results

Locomotor activity significantly increased after the administration of methamphetamine (2.0 – 20 mg/kg). In particular, 2.0 mg/kg of methamphetamine potently increased locomotor activity, especially with frequent rearing and non-stereotypic hyperlocomotion throughout the entire test cage (Fig. 1: bottom panel). High dose of methamphetamine (20 mg/kg) induced SIB, such as skin-picking and biting, and such SIB was observed in 6 of 7 mice. Peak SIB appeared from 30 to 60 min after the administration of high doses of methamphetamine (Fig. 1: top panel).

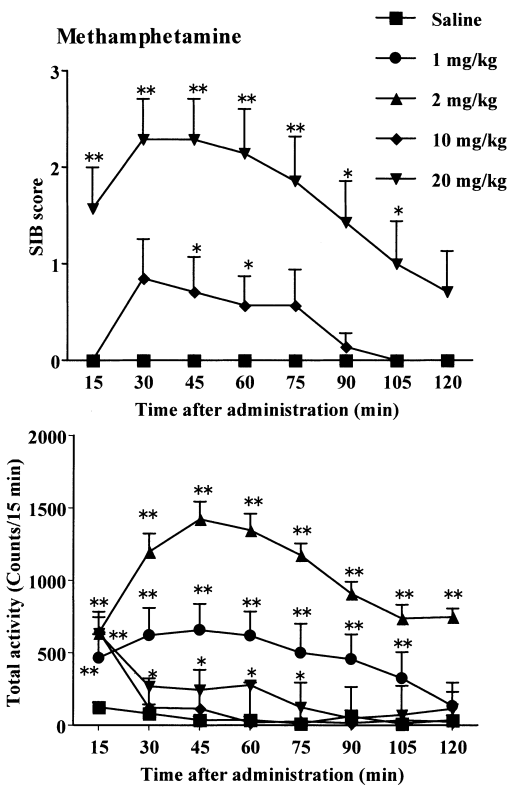

Fig. 1. Effects of methamphetamine on self-injurious behavior (SIB: top panel) and spontaneous locomotor activity (bottom panel) in mice. Each point represents the mean counts with S.E.M. of 7 animals. **P*<0.05, ***P*<0.01, *vs* saline control.

In combination tests, methamphetamine-induced SIB and initial hyperlocomotion were significantly attenuated by a high dose of SCH23390 (1.0 mg/kg) (Fig. 2: left). Similar to these results with SCH23390, a high dose of haloperidol (1.0 mg/kg) also significantly and completely attenuated methamphetamine-induced SIB and initial hyperlocomotion. Haloperidol (0.1 mg/kg) significantly attenuated methamphetamine-induced SIB. However, unlike with a high dose of haloperidol (1.0 mg/kg), this lower dose of haloperidol significantly enhanced locomotor activity in combination with methamphetamine (Fig. 2: right).

Figure 3 shows the effects of 5-HT-related compounds on methamphetamine-induced SIB and locomotor activity. 5-HTP dose-dependently and significantly attenuated methamphetamine-induced SIB. Furthermore, the highest dose of 5-HTP completely attenuated methamphetamine-induced SIB, and slight hyperactivity accompanied by 5-HT syndrome, such as head-weaving and head tremor, was observed with the combination of methamphetamine and 5-HTP (increased locomotor activity might be reflected by 5-HT syndrome, especially head-weaving). While fluvoxamine and MDMA significantly attenuated methamphetamine-induced SIB, dose-dependency was not observed. The doses of fluvoxamine and MDMA that significantly

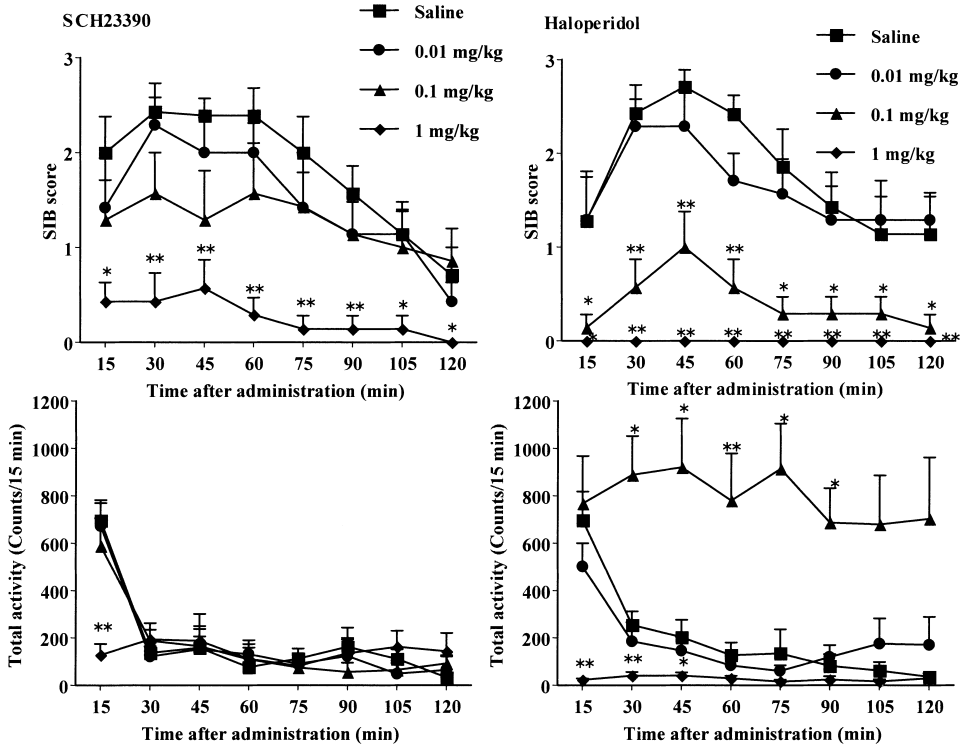

Fig. 2. Effects of SCH23390 and haloperidol on methamphetamine (20 mg/kg)-induced SIB (top panel) and locomotor activity (bottom panel) in mice. Each point represents the mean counts with S.E.M. of 7 animals. **P*<0.05, ***P*<0.01, *vs* saline control.

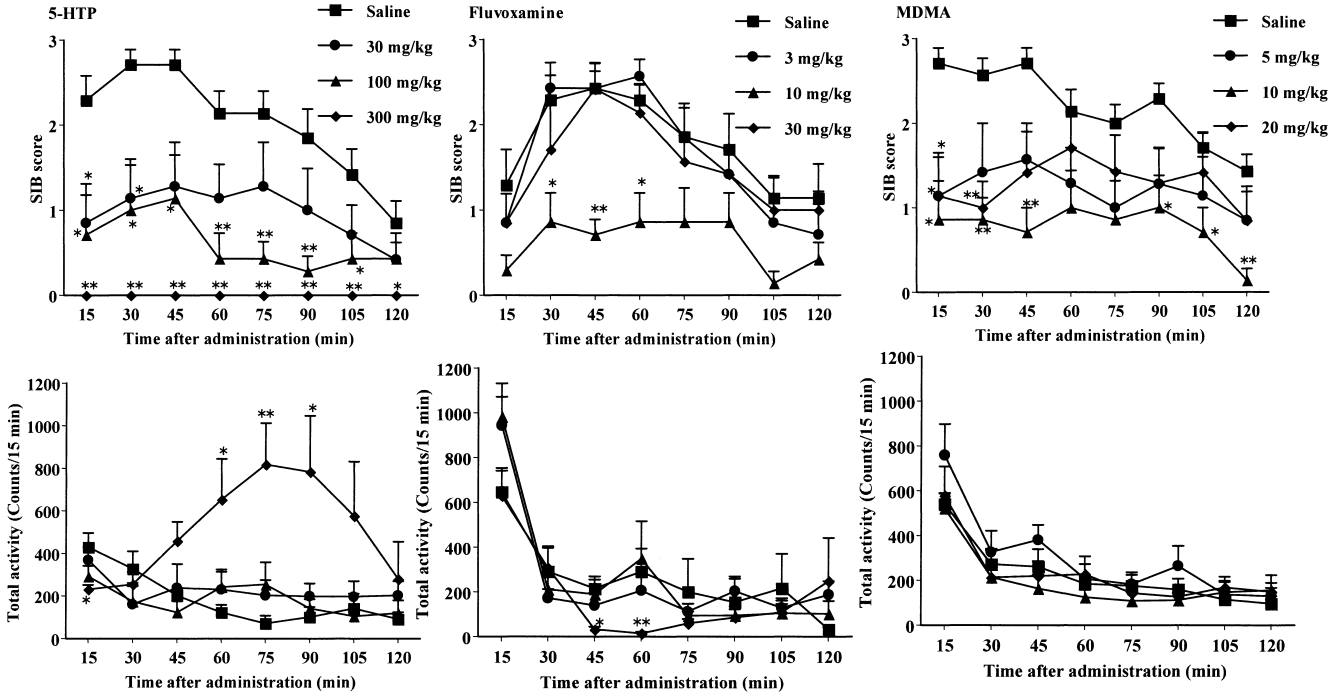

Fig. 3. Effects of 5-hydroxytryptophan (5-HTP), fluvoxamine, and MDMA on methamphetamine (20 mg/kg)-induced SIB (top panel) and locomotor activity (bottom panel) in mice. Each point represents the mean counts with S.E.M. of 7 animals. *P<0.05, **P<0.01, *vs* saline control.

attenuated methamphetamine-induced SIB did not affect any other behavior induced by methamphetamine.

Discussion

The present study showed that dopamine receptor antagonists significantly attenuated methamphetamine-induced SIB. These results indicate that the dopaminergic system plays a crucial role in methamphetamine-induced SIB. Furthermore, a 5-HT precursor (5-HTP), SSRI (fluvoxamine), and 5-HT releaser (MDMA) also attenuated methamphetamine-induced SIB, suggesting that the stimulation of 5-HT receptors plays an inhibitory role in high-dose methamphetamine-induced SIB in mice. Therefore, 5-HT-related compounds may be useful for treating human SIB.

In the present study, the initial hyperlocomotion induced by 20 mg/kg of methamphetamine was abolished by high doses of SCH23390, a D_1-receptor antagonist, and haloperidol, a D_2-receptor antagonist, indicating that the hyperlocomotion induced by a high dose of methamphetamine is mediated by the activation of D_1- and D_2-receptors. Methamphetamine caused frequent rearing and non-stereotypic hyperactivity, and higher doses of methamphetamine decreased locomotor activity with continuous SIB in the present study. However, we also found that a medium dose of haloperidol (0.1 mg/kg), but not SCH23390, potently increased locomotor activity in combination with 20 mg/kg of methamphetamine. Furthermore, haloperidol (0.1 mg/kg) potently attenuated methamphetamine-induced SIB. These results suggest that excess dopaminergic activation, especially the activation of dopamine D_2-receptors, may be involved in the decrease in locomotor activity induced by a high dose of methamphetamine. On the other hand, these results strongly indicate that the mechanisms that underlie methamphetamine-induced SIB and hyperlocomotion are different. It is well known that the hyperlocomotion induced by psychostimulants is mediated by the mesolimbic dopaminergic system, whereas stereotyped behavior is mediated by the nigrostriatal dopaminergic system. Furthermore, it has been reported that haloperidol preferentially affects the nigrostriatum dopaminergic system rather than the medolimbic dopaminergic system (21, 22). These results indicate that the nigrostriatal dopaminergic system plays a crucial role in methamphetamine-induced SIB and decrease in locomotor activity in mice and that the remnant dopamine which could activate the mesolimbic dopaminergic system rather than nigrostriatum dopaminergic system may induce hyperlocomotion in combination with methamphetamine plus 0.1 mg/kg of haloperidol. Whereas, 1.0 mg/kg of haloperidol completely attenuated behaviors, such as locomotion and SIB, and

these attenuations may be mediated by the inhibition of the dopaminergic system (20). Therefore, we speculate that the occurrence of the phenotype of dopamine-related behaviors may be mediated via actions in the mesolimbic and/or nigrostriatal dopaminergic systems associated with the dose of methamphetamine.

In the present study, high doses of methamphetamine induced hypolocomotion. It has been noted that the increases in dopamine activation in the nucleus accumbens or striatum induced by abused drugs are not accompanied by proportionate changes in behavioral outcomes (23 – 25). However, the present results showed that 20 mg/kg of methamphetamine-induced hypoactivity was significantly increased by a low dose of haloperidol. These results suggest that excess dopaminergic activation may be involved in the effect of methamphetamine on locomotor activity in mice. Therefore, we propose that appropriate dopaminergic activation (between the nucleus accumbens and striatum) might engender corresponding behavioral outcomes.

A previous study demonstrated that sulpiride, a D_2-receptor antagonist, did not affect methamphetamine-induced SIB in mice (16). On the other hand, Wagner et al. (26) recently showed that risperidone (a 5-HT_2/D_2-receptor antagonist), but not haloperidol, attenuated amphetamine-induced SIB in mice. These previous results prompt us to ask why haloperidol attenuated methamphetamine-induced SIB in the present study. With regard to these discrepant results, a large growing body of evidence has demonstrated that there are clear strain differences in some behavioral effects. Both Shishido et al. (16) and Wagner et al. (26) used BALB/c mice, whereas we used ddY mice. In fact, hyperlocomotion was not observed with the administration of psychostimulants in BALB/c mice, unlike in other strains (27 – 30). On the other hand, it has been demonstrated that haloperidol and risperidone/sulpiride have different effects on the dopaminergic system (31 – 34). Such differences, especially strain differences, may explain these discrepant results.

Patients with de Lange syndrome commonly show lowered whole-blood 5-HT levels (35), whereas in Tourette's syndrome, the ratio of 5-HT to dopamine metabolites is reduced (36). A previous study (16) as well as the present study showed that 5-HTP could completely attenuate methamphetamine-induced SIB. Furthermore, fluvoxamine and MDMA attenuated methamphetamine-induced SIB in the present study. These results may reflect the clinical finding that 5-HT-related compounds may be beneficial for alleviating SIB in some populations (3, 14, 15). However, dose-dependency was not observed with fluvoxamine and MDMA. In contrast, paroxetine, another SSRI, aggravated pemoline-induced SIB (37). A recent study showed that SSRIs and MDMA could enhance the release of dopamine from nerve terminals (38, 39); therefore, high doses of SSRIs and MDMA could strengthen the methamphetamine's effects as a dopamine receptor indirect agonist. Such a mechanism, at high doses, might contribute to the weakened effects of fluvoxamine and MDMA in methamphetamine-induced SIB in the present study.

The 5-HT-receptor superfamily is composed of 14 subtypes that have been classified based on gene structure, amino acid sequence homology, and intracellular signaling cascades (40). All of the 5-HT receptors, except the 5-HT_3-receptors, couple to guanine nucleotide-binding proteins (G proteins) to produce second messengers. Five families of G protein-coupled 5-HT receptors (5-HT_1, 5-HT_2, 5-HT_4, 5-HT_6, and 5-HT_7) regulate two major intracellular second-messenger pathways: those involving adenylate cyclase and phospholipase C (41). Activation of these receptor subtype(s) may attenuate methamphetamine-induced SIB by the 5-HT-related compounds used in the present study. Nevertheless, there is no direct evidence regarding the mechanism by which 5-HT acts on SIB in the central nervous system. Therefore, further examination is needed to reveal the underlying mechanism(s) by which endogenous 5-HT could attenuate methamphetamine-induced SIB in mice.

In summary, the present study showed that the dopaminergic system, especially the activation of both D_1- and D_2-receptors, plays a crucial role in methamphetamine-induced SIB. Furthermore, the activation of endogenous 5-HT may be useful for treating destructive behavior, such as SIB.

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